Atty. Dkt. No. 7381.111

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Anticipated Classification of
this application:
Class _____, Subclass _____

Prior Application:

Examiner C. Aulakh
Art Unit 1612

Box Patent Application
Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

This is a request for filing a [X] continuation [ ] divisional application under 35 U.S.C. 120 and/or 37 C.F.R. 1.60, of pending prior application serial no(s). 08/948,319 filed October 10, 1997 (soon to be issued as U.S. Patent No. 5,942,540); which is a continuation-in-part of 08/632,338 filed on April 10, 1996 (now U.S. Patent No. ~~XXXXXXXXXXXX~~ 5,728,728), of Walter E. Kozachuk, for METHODS OF PROVIDING SYMPTOMATIC AND PROPHYLACTIC NEUROPROTECTION all of which are incorporated herein by reference.

1. [X] Enclosed is a copy of the prior application(s), including the oath or declaration as originally filed and an affidavit or declaration verifying it as a true copy.

2. [ ] Enclosed is a Request for Extension of Time for (1/2/3/4) month(s).

3. The filing fee is calculated below:

CLAIMS AS FILED IN THE PRIOR APPLICATION,
LESS ANY CLAIMS CANCELLED BY AMENDMENT BELOW

	(Col. 1)	(Col. 2)	Small Entity		Other Than A Small Entity	
FOR:	No. Filed	No. Extra	Rate	Fee	Rate	Fee
Basic				$380		$760
Total Claims	-20=	*	x $9	$	x $18	$
Indep. Claims	-3=	*	x $39	$	x $78	$
Mult. Dep. Claim Present			+ $130		+ $260	
			Total	$	Total	$

* If the difference in col. 1 is less than zero, enter "0" in col. 2

4. [ ] The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Account No. 50-0548. A duplicate copy of this sheet is enclosed.

5. [ ] A check in the amount of $_____ is enclosed.

5a. [X] This Application is being filed according to Rule 53.

6. [X] Cancel in this application original claims 1-3 and 7-8 of the prior application before calculating the filing fee.

7. [X] Please amend the specification by inserting before the first line the sentence: --This is a [X] continuation, [ ] division of application serial no(s). 08/948,319 filed 10/10/97 (soon to be issued as U.S. Pat. No. 5,942,540); which is a CIP of _____, ~~filed~~ ~~XXXXX~~ 08/632,338 filed 4/10/96 (now U.S. Pat. No. 5,728,728) all of which are ~~XXX~~ incorporated herein by reference.--

8. [ ] Transfer the drawings from the prior application to this application and abandon said prior application as of the filing date accorded this application. A duplicate copy of this sheet is enclosed for filing in the prior application file.

8a. [ ] Informal/formal drawings are enclosed.

8b. [ ] Priority of application serial no(s).
_____, filed on
_____, in
_____
is claimed under 35 U.S.C. 119.

[ ] The certified copy has been filed in prior application serial no(s).
_____, filed
_____.

9. [ ] The prior application(s) is(are) assigned of record to

_____

10. [X] The power of attorney in the prior application(s) is/are to:

Myers, Liniak & Berenato

a. [X] The power appears in the original papers in the prior application(s).

b. [ ] Since the power does not appear in the original papers, a copy of the power in the prior application is enclosed.

c. [X] Address all future communications to:

Joseph A. Rhoa, Esquire
Liniak, Berenato, Longacre & White
6550 Rock Spring Drive, Ste. 240
Bethesda, Maryland 20817
(301) 896-0600

11. [X] A preliminary amendment is enclosed. Claims added by this amendment have been properly numbered consecutively beginning with the number next following the highest numbered original claim in the prior application.

12. [X] I hereby verify that the attached papers are a true copy of prior application serial no(s). 08/948,319 filed 10/10/97 (soon to be issued a U.S. Pat. No. 5,942,540); which is a CIP of 08/632,338 as originally filed on 4/10/96 (now U.S. Pat. No. 5,728,728) all of which are incorporated herein by reference.

The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: 8/20/99

Joseph A. Rhoa, Esquire
Reg. No. 37,515
Attorney for Applicant(s)

[ ] inventor(s)
[ ] Assignee of complete interest
[X] Attorney or agent of record
[ ] Filed under Rule 34(a)

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PTO/SB/09 (11-90)

VERIFIED STATEMENT CLAIMING SMALL ENTITY STATUS (37 CFR 1.9(f) & 1.27(b))--INDEPENDENT INVENTOR	Docket Number (Optional) 7349.112

Applicant or Patentee: Walter E. Kozachuk

Serial or Patent No.: 08/948,319

Filed or Issued: Oct. 10, 1997

Title: METHODS OF PROVIDING SYMPTOMATIC AND PROPHYLACTIC NEUROPROTECTION

As a below named inventor, I hereby declare that I qualify as an independent inventor as defined in 37 CFR 1.9(c) for purposes of paying reduced fees to the Patent and Trademark Office described in:

[X] the specification filed herewith with title as listed above.

[ ] the application identified above.

[ ] the patent identified above.

I have not assigned, granted, conveyed or licensed and am under no obligation under contract or law to assign, grant, convey or license, any rights in the invention to any person who would not qualify as an independent inventor under 37 CFR 1.9(c) if that person had made the invention, or to any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or a nonprofit organization under 37 CFR 1.9(e).

Each person, concern or organization to which I have assigned, granted, conveyed, or licensed or am under an obligation under contract or law to assign, grant, convey, or license any rights in the invention is listed below:

[X] No such person, concern, or organization exists.

[ ] Each such person, concern or organization is listed below.

Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27)

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

Walter E. Kozachuk		
NAME OF INVENTOR	NAME OF INVENTOR	NAME OF INVENTOR
Signature of inventor: Walter E. Kozachuk MD	Signature of inventor	Signature of inventor
Date: 3-9-98	Date	Date

PTO/SB/09 (11-90) Patent and Trademark Office; U.S. DEPATMENT OF COMMERCE

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	:	
	:	
WALTER E. KOZACHUK	:	Art Unit: 1612
	:	
Serial No.: To Be Assigned	:	Examiner: C. Aulakh
	:	
Filed: Concurrently	:	
	:	Atty. Dkt. No. 7349.111
For: METHODS OF PROVIDING SYMPTOMATIC AND PROPHYLACTIC NEUROPROTECTION	:	

Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

PRELIMINARY AMENDMENT

IN THE CLAIMS:

Please cancel claims 1-3 and 7-8.

REMARKS

Prior to initial examination of the instant application, please amend the specification as set forth above. No new matter has been added.

Respectfully submitted,

Joseph A. Rhoa, Esquire
Registration No. 37,515
Attorney for Applicant(s)

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Atty. Dkt. No.: 7349.112

METHODS OF PROVIDING SYMPTOMATIC AND PROPHYLACTIC NEUROPROTECTION

Inventor: Walter E. Kozachuk

This is a continuation-in-part of copending application Ser. No. 08/632,338 filed April 10, 1996, the disclosure of which is incorporated herein by reference.

METHODS OF PROVIDING SYMPTOMATIC AND PROPHYLACTIC NEUROPROTECTION

FIELD OF THE INVENTION

The present invention relates to pharmaceutical compositions whose mechanisms of action include at least antagonism at the glycine site on the NMDA (N-methyl-D-aspartate) receptor complex, and to methods for prophylaxis, attenuation, or prevention of acute or chronic neuronal damage in various systemic or neurological diseases, conditions, or procedures.

BACKGROUND OF THE INVENTION

The major excitatory neurotransmitters in the central nervous system is L-glutamine and L-aspartate. Classification of the excitatory receptors include the AMPA, kainate and NMDA receptors. The NMDA receptor is located on the neuronal cell surface and is composed of multiple binding sites which regulate Ca++ homeostasis. The glycine and glutamate binding sites are

allosterically linked at the NMDA receptor complex. Glutamate is the principal excitatory neurotransmitter in the brain and has an integral role in neurologic function including cognition, memory, movement and sensation. Glutamate has also been implicated in the pathogenesis of multiple acute and chronic neurological diseases.

Felbamate (2-phenyl-1,3-propanediol dicarbamate) is a known pharmaceutical compound and is described in U.S. Patent No. 2,884,444. Felbamate has multiple actions on the nerve cell of which one is a glycine site antagonist at the NMDA receptor. See U.S. Patent Nos. 4,978,680; 5,082,861; 5,292,772; 4,868,327; and 5,256,690.

Felbamate is a modulator of NMDA function by a glycine site antagonist mechanism but has multiple mechanisms of action. These include interaction at the AMPA/kainate receptor, facilitating GABA function, modulation of the Na+ channel, interaction at both of the metabotropic and muscarinic receptors, as well as the L-type calcium channel.

Excessive stimulation of the NMDA receptor by excitatory amino acids or neurotoxic mediators of inflammation is believed to be the etiology of multiple

acute and chronic neurological diseases. Sudden toxic elevations of glutamate in acute neurological disorders or increased nerve cell vulnerability by abnormal bioenergetic metabolism in chronic disorders are possible mechanisms. Thus, NMDA exictotoxicity may represent a final common pathway for neuronal death in both acute and chronic neurological disease.

Subsequent to the approval of Felbamate, in 1994 there were reports of aplastic anemia and hepatic failure. These adverse events may have been due to drug interaction.

OBJECT OF THE INVENTION

One of the objects of the present invention is to provide compositions and methods for the treatment of acute and chronic disorders that involve excessive activation of the NMDA receptor.

Another object of the present invention is to provide a method for attenuation or prevention of neuronal cell death caused by excessive activation of the NMDA receptor by administering the drug prophylactically

and chronically when the patient has asymptomatic or pre-clinical systemic or neurological disease.

Another object of the present invention is to provide compositions and methods effective to prevent, control, or attenuate acute and chronic neuronal injury and death from systemic or neurological disease.

A further objective of the present invention is to provide compositions and methods for the prevention and control of acute and chronic systemic or neurological disorders that involve excessive activation of the NMDA receptor, which compositions are relatively non-toxic, have a high degree of effectiveness and continue to produce a therapeutic response over a long duration of time.

An additional object of the present invention is the treatment of the chronic neulogical condition called spasticity by the administration of a compound that has at least the property of antagonizing the glycine-site at the NMDA receptor.

SUMMARY OF THE INVENTION

The subject invention relates to methods for treating acute and chronic neurological diseases and reducing or preventing neuronal cell death in both systemic and neurological diseases, in mammals including humans, employing a drug whose mechanism of action is at least partially mediated through a strychnine-insensitive glycine receptor mechanism. The antagonists are administered intravenously or orally, acutely or chronically, to prevent or attenuate neuronal damage and death. Advantageously, the drug is administered prophylactically and chronically when the patient is at risk for asymptomatic or pre-clinical systemic or neurological disease, or when the patient undergoes a vascular procedure which have a high risk for neuronal cell injury or death.

This invention also relates to a method of reducing or preventing neuronal cell injury or death when the glycine-site antagonist, felbamate, is administered prophylatically and chronically in a mammal, or a human.

This invention also relates to a method of reducing or preventing neuronal cell injury or death when the

glycine-site antagonist, felbamate, is used as monotherapy or polytherapy, in a human or mammal.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to pharmaceutical compositions and to methods for the prevention and attenuation of systemic disorders, acute and chronic neurological disorders, that involve the excessive activation of the NMDA receptor. Advantageously, the present invention relates to methods for neuroprotection in systemic and neurological disease through the administration of therapeutic compositions which contain, for example, the active ingredient 2-phenyl-1,3-propanediol dicarbamate, commonly known as felbamate. The compounds, such as felbamate, may be administered prophylactically, acutely, subacutely, or chronically via the intravenous, oral or rectal route. This compound has multiple mechanisms of action, one of which is a glycine-site antagonist at the NMDA receptor. Felbamate is able to inhibit the toxic effects of high glutamate concentrations while sparing the physiologic functions of

the NMDA receptor, and thus can be safely administered chronically as monotherapy to humans.

Neuroprotection may be defined as increasing the tolerance of the glia and neurons of the brain and spinal cord to excessive NMDA activation which results in the prevention of neuronal cell death and promoting functional neuronal recovery, rather than just protecting neurons from ischemia (Fisher M., Stroke 25:1075-1080, 1994). Prophylactic neuroprotection will be administered to populations at high-risk for neuronal cell death. These would include (1) short term neuroprotection both prior to and post high-risk invasive, vascular or other procedures whose adverse event would produce neuronal injury or death, (2) chronic neuroprotection for high-risk populations with systemic disease or multiple cerebrovascular risk factors which increase the probability of neuronal cell injury or death, and (3) concomitant neuroprotection with other medications administered for specific systemic or neurological diseases which increase the risk for neuronal cell injury or death.

Several populations have a high long-term risk for neuronal cell injury or death which include vascular risk factors (such as obesity and hypertension), transient ischemic attacks, atrial fibrillation and other cardiac disorders, and asymptomatic carotid stenosis. In addition, there is a high risk of further additional neuronal cell injury or death after patients suffer a minor stroke. Patients with systemic diseases which increase the risk of neuronal cell injury or death have therapies directed specifically at the underlying disease and may require a concomitant neuroprotectant medication.

The short-term neuroprotection group includes patients undergoing vascular procedures such as coronary artery bypass graft surgery, carotid endarterectomy or other endovascular therapy which carry a high risk for embolic or ischemic complications resulting in neuronal cell injury or death. Depending on the individuals cerebrovascular risk factors, felbamate would be administered both pre- and post-procedure for a variable or chronic length of time.

The population for long-term felbamate administration would include patients with a high

cerebrovascular risk-factor profile such as chronic hypertension, collagen vascular disease, atrial fibrillation, previous transient ischemic attack, etc.

The concomitant neuroprotection group includes those patients with a high cerebrovascular risk-factor profile from systemic disorders such as diabetes, hyperlipidemia, hypertension, collagen vascular disease, etc. in which felbamate is co-administered for neuroprotection with other medications which control and treat the underlying disease.

<u>COMPOUNDS OF THE INVENTION</u>

Compounds of the invention include felbamate, quinoxalinediones including the ACEA compounds (1011, 1021, 1031, 1328) ACPC (1-aminocyclopropane carboxylic acid), 1,4 dihydroquinoxaline-2,3-diones, 4-hydroxy-2-quinalones, 4-amino-2-carboxytetrahydro-quinolines, trans-4-hydropipecolic acid-4-sulfate, and other compounds whose mechanism of action includes at least glycine-site antagonism at the NMDA receptor

THERAPEUTIC USES OF THE COMPOUNDS OF THE INVENTION

Felbamate as monotherapy and other antagonists at the glycine site of the NMDA receptor are useful in the reduction or prevention of neuronal cell injury or cell death in systemic or neurologic diseases as well as patients with cerebrovascular risk factors, in which glutamate or other inflammatory neurotoxins and excitatory amino acids are involved in the pathophysiology. Felbamate is also useful for the treatment of spasticity due to its antagonism at the glycine-site at the NMDA receptor and its potentiation of GABA transmission.

OBESITY

Obesity is a common human disorder which affects 10-15% of the population, of which up to 5% may be severely obese. It is estimated that the mortality from obesity is between 300,000 to 400,000 per annum. Obesity is commonly measured by the BMI (body mass index) which is the weight in kilograms divided by the height in meters squared. The degree of obesity is determined by

comparisons against standard deviations above the means for males and females.

The male pattern of obesity is referred to as the android pattern in which the fat is distributed in the upper body while the female pattern is the gynecoid in which the body fat is distributed below the waist. These patterns appear to be related to the hormones testosterone and estrogen, respectively. Android obesity increases the risk of hypertension, cardiovascular disease, hyperinsulinemia, and diabetes mellitus.

The etiology of obesity is unknown but occurs when energy intake exceeds energy expenditure. Appetite is controlled by the ventromedial hypothalamus and complex interconnections with the limbic system and other portions of the brain. The amount of body fat has some genetic predisposition and rare genetic diseases such as Prader-Willi, syndrome, Laurence-Moon-Biedl syndrome, the Alstrom syndrome, the Cohen syndrome, the Carpenter syndrome, and Blount's disease are associated with obesity.

Complications of obesity include insulin resistance, diabetes mellitus, hypertension, cardiovascular disease,

cerebral hemorrhage, pseudotumor cerebri, hyperlipidemia, respiratory problems, sleep apnea, venous circulatory disease, cancer, cholecystitis, and osteoarthritis.

Recent neurochemical research has implicated leptin, GLP-1 (glucagon-like peptide 1) and neuropeptide-Y in the control of appetite. Leptin is a natural appetite suppressant which is released from adipose cells, travels to the brain and appears to exert some control over appetite and long term weight control. A defective leptin receptor has been postulated to be involved in obese patients. GLP-1, a brain hormone which promotes satiety, is believed to regulate short-term appetite. Neuropeptide-Y is a potent stimulator of appetite whose effects can be blocked by leptin and GLP-1. The complete interaction of these compounds remains to be elucidated.

Felbamate has been known to induce anorexia in patients treated with epilepsy. In a study of felbamate as add-on therapy in partial epilepsy in children, weight loss was transient and returned to normal after twenty weeks (Carmant J., Pediatr 125:481-486, 1994). Weight loss of 4-5% was noted in patients on felbamate monotherapy (Faught E., Neurology 43:688-692, 1993). The

mechanism is unclear and the weight loss has been attributed to nausea and vomiting and the withdrawal of other medications whose side effects are weight gain (Sachdeo R, Ann Neurol 32:386-392, 1992). We suggest a novel hypothesis that weight loss from felbamate is due to NMDA receptor modulation in the hypothalamic structures involved in appetite control.

Felbamate, administered chronically to humans in oral doses of from about 100-15,000 mg/day, advantageously from about 1200-7200 mg/day (serum levels ranging from about 25-300 ug/ml), is efficacious in producing weight loss in obesity, type-II diabetes, and other genetic obesity disorders. The weight loss will subsequently attenuate neuronal cell injury and death from the cerebrovascular complications of obesity.

SPASTICITY

Spasticity is a human motor disorder manifested by an increase in muscle tone and an exaggeration of deep tendon reflexes due to lesions of the corticospinal system. The spasticity is proportional to the rate and degree of stretch placed on the muscle. The most common

causes are multiple sclerosis and spinal cord injury. Spasticity produces multiple medical complications, pain, and depression.

The etiology of spasticity is a decrease or malfunctioning of inhibitory mechanisms in the spinal cord leading to hyper-excitability of the tonic stretch and other reflexes. The mechanism may involve a decrease in both presynaptic GABA-ergic inhibition and postsynaptic inhibition. Noradrenergic receptors become supersensitive distal to spinal cord injury which is the rationale for using alpha-2 agonists as a treatment in spinal cord injury. GABA and glycine are the main inhibitory neurotransmitters in the spinal cord. Glycine acts at both the strychnine-insensitive and strychnine-sensitive receptors, the latter being more common in the spinal cord.

The pharmacotherapy of spasticity is directed at the potentiation of inhibitory transmission within the spinal cord, such as the mediation of presynaptic inhibition by GABA. Excitatory amino acids (EAA) increase spasticity and non-competitive NMDA antagonists depress spinal polysynaptic reflexes by inhibiting the release of EAA

(Schwarz M., In Thilman AF, Ed. Spasticity, pp 85-97, 1993). Felbamate has both GABA enhancing properties and glycine-site strychnine insensitive antagonist properties which suggests efficacy in the treatment of spasticity.

Felbamate, administered chronically in oral doses of from about 100-15,000 mg/day, advantageously from about 1200-7200 mg/day (serum levels ranging from 25-300 ug/ml), is efficacious in reducing spasticity from both supraspinal and spinal lesions.

<u>SYMPTOMATIC DEPRESSION</u>

Depression or mood disorders are psychopathologic states in which a disturbance of mood is either a primary determinant or constitutes the core manifestation. Secondary depression is an affective disorder caused by a systemic or neurological disease. Examples of neurologic diseases include multiple sclerosis, Parkinson's disease, head trauma, cerebral tumors, post-stroke, early dementing illness, and sleep apnea etc. while systemic diseases include infections, endocrine disorders, collagen vascular diseases, nutritional deficiencies and neoplastic disease. Secondary depression is common in

post-myocardial infarct patients and carry a mortality three times that of non-depressed post-myocardial patients.

Felbamate, administered chronically in oral doses of from about 100-15,000 mg/day, advantageously from about 1200-7200 mg/day (serum levels ranging from 25-300 ug/ml), is efficacious in reducing secondary symptomatic depression in both human systemic and neurologic diseases.

POST-MYOCARDIAL INFARCTION NEUROPROTECTION

Patients with myocardial infarction are at a high risk for cardiac arrest resulting in global ischemia and causing neuronal injury, infarction and brain death. Other brain complications include cardiac embolism to the brain resulting in ischemic brain damage.

Felbamate has been to shown to be effective in preventing neuronal cell death when administered post-hoc (Wasterlain, C.G. Neurology 43:2303-2310, 1993; Shuaib, A. Brain Res. 727:65-70, 1996) as well as delayed cellular necrosis and delayed neuronal apoptosis in animal models of ischemia (Wasterlain, C.G., Stroke

27:1236-1240, 1996). These results show the efficacy of felbamate in preventing ischemic brain damage. All patients who have myocardial infarction are potentially at risk for global ischemia and cardiac embolism and should be placed on prophylactic felbamate to prevent and reduce neuronal cell death, delayed cellular necrosis and neural apoptosis.

Felbamate, administered chronically and prophylactically in oral doses of from about 100-15,000 mg/day, advantageously from about 1200-7200 mg/day (serum levels ranging from 25-300 ug/ml), is efficacious in preventing and reducing neuronal human cell injury and death from ischemia and embolism in patients with myocardial infarction.

VASCULAR PROCEDURES

Certain invasive cardiovascular and peripheral vascular procedures are associated with a risk of both ischemic and embolic cerebrovascular damage. These procedures include coronary artery bypass graft surgery, cardiac valvular replacement, cardiac transplant, carotid endarterectomy, cerebral and peripheral aneurysmectomy,

arterio-venous malformation resection, and endovascular therapy.

Felbamate administered pre- and post-vascular procedure would allow patients to have maximum neuroprotection prior to their exposure of such cerebrovascular risks.

Felbamate, administered acutely or chronically and prophylactically pre-vascular procedure and chronically post-vascular procedure in oral doses of from about 100-15,000 mg/day, advantageously from about 1200-7200 mg/day (serum levels ranging from 25-300 ug/ml), is efficacious in preventing and reducing neuronal human cell injury and death in patients undergoing central and peripheral vascular procedures.

<u>PROPHYLAXIS IN PATIENTS WITH CEREBROVASCULAR RISK FACTORS</u>

Several populations are at a high risk for insidious neuronal cell death, silent cerebral ischemia, and subsequent cerebral infarction. Individual risk factors, which may be present in various combinations, include hypertension, diabetes, atrial fibrillation, underlying cardiac disease, hyperlipidemia, collagen vascular

disease, and transient ischemic attacks. A recent study has shown that asymptomatic hypertensive patients have evidence of cerebral neuronal degeneration (Salerno J.A., Hypertension 20:3340-348, 1992; Mentis M.J., Stroke 25:601-607, 1994). We hypothesize an up-regulation of cytokines which produce toxic inflammatory mediators such as the NMDA agonist quinolinic acid. This results in chronic overstimulation of the NMDA receptor producing neuronal cell death. Felbamate is a candidate for prophylactic neuroprotection since it is a glycine-site NMDA antagonist which easily crosses the blood brain barrier and can be safely administered chronically as monotherapy.

Felbamate, human administered prophylactically and chronically in asymptomatic patients with cerebrovascular risk factors in oral doses of from about 100-15,000 mg/day, advantageously from about 1200-7200 mg/day (serum levels ranging from 25-300 ug/ml), is efficacious in preventing and reducing neuronal cell injury and death in populations with cerebrovascular risk factors.

WHAT IS CLAIMED IS:

1. A method of protecting neuronal cells from the consequences of obesity in a mammal, the method comprising administering to the mammal a neuronal cell protecting amount of an antagonist at the glycine site of the NMDA receptor.

2. A method of treating the symptoms and complications of spasticity in a mammal by administering to the mammal a neuronal cell protecting amount of an antagonist at the glycine site of the NMDA receptor.

3. A method of treating symptomatic depression in systemic or neurological diseases by administering to a mammal, a neuronal cell protecting amount of an antagonist at the glycine site of the NMDA receptor.

4. A method of reducing or preventing neuronal cell injury or death due to ischemia or embolism in post-myocardial infarction patients by administering a neuronal cell protecting amount of an antagonist at the glycine site of the NMDA receptor, to a mammal.

5. A method of reducing or preventing neuronal cell injury or death due to ischemia or embolism in invasive vascular procedures patients by administering a neuronal cell protecting amount of an antagonist at the glycine site of the NMDA receptor, both pre-procedure and post-procedure for chronic periods, to a mammal.

6. A method of reducing or preventing neuronal cell injury or death due to excessive NMDA stimulation in patients with cerebrovascular risk factors by prophylactically administering a neuronal cell protecting amount of an antagonist at the glycine site of the NMDA receptor, to a mammal.

7. A method of treating the chronic neurological condition of spasticity by administering a therapeutic amount of antagonist at the glycine site of the NMDA receptor, to a mammal.

8. The method of claim 1, wherein the antagonist is felbamate.

ABSTRACT OF THE DISCLOSURE

Methods are disclosed for prophylactically and chronically preventing symptomatic depression, neuronal cell injury and cell death in systemic and neurological conditions, populations with cerebrovascular risk factors, and invasive vascular procedures, employing a glycine-site antagonist at the NMDA (N-methyl-D-aspartate) complex e.g., 2-phenyl-1,3-propanediol dicarbamate (felbamate).

PTO/SB/01 [illegible]-301

DECLARATION FOR PATENT APPLICATION

Docket Number (Optional)
7349.112

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled METHODS OF PROVIDING SYMPTOMATIC AND PROPHYLACTIC NEUROPROTECTION, the specification of which is attached hereto unless the following box is checked:

[X] was filed on 10/10/97 as United States Application Number or PCT International Application Number 08/948,319 and was amended on [illegible] (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, § 1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, § 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s) (Number)	(Country)	(Day/Month/Year Filed)	Priority Claimed
			☐ Yes ☐ No
			☐ Yes ☐ No
			☐ Yes ☐ No

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, § 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application.

(Application Number)	(Filing Date)	(Status – patented, pending, abandoned)
08/632,338	4/10/96	pending

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: Geoffrey R. Myers, Reg. #24,897; Thomas P. Liniak, Reg. #33,415; Joseph W. Berenato, III, Reg. #30,546; Joseph A. Rhoa, Reg. #37,515; Elaine Papavasiliou, Reg. No. 40,117

Address all telephone calls to Joseph A. Rhoa, Esq. at telephone number (301) 365-8000

Address all correspondence to Joseph A. Rhoa, Esquire
Myers, Liniak & Berenato
6550 Rock Spring Drive, Ste. 240
Bethesda, Maryland 20817

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first inventor (given name, family name) Walter E. Kozachuk
Inventor's signature Walter E. Kozachuk MD Date 3-9-98
Residence 11403 Cam Court, Kensington, MD 20895-1313 Citizenship U.S.A.
Post Office Address Same

Full name of second joint inventor, if any (given name, family name)
Second Inventor's signature Date
Residence Citizenship
Post Office Address

☐ Additional inventors are being named on a separate sheet attached hereto.